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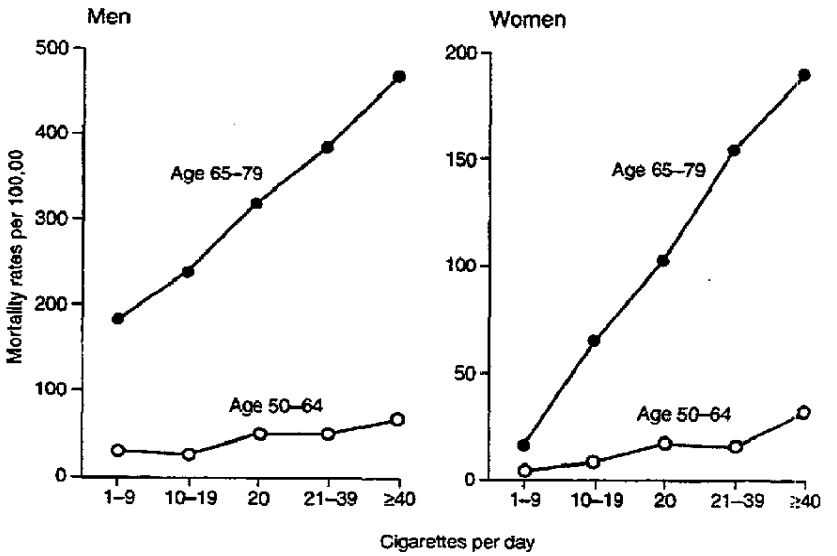
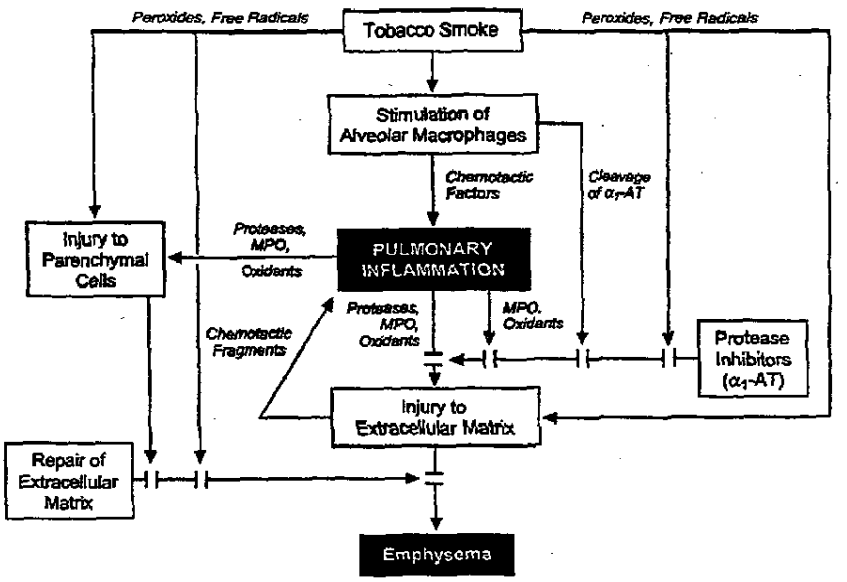
Figure 14-3 Mortality Rates



NOTE: Graphs showing relationships between mortality rates from COPD among current white smokers by level of cigarette consumption. Plotted are standardized mortality rates per 100,000 adjusted within 15-year age-specific rates to 1980 U.S. standard population for men and women.

SOURCE: Data for figure gathered from Burns, D. M., Shanks, T.G., Choi, W., Thun, M.J., Heath, C.W., Garfinkel, L. The American Cancer Society Cancer Prevention Study: 12-Year Follow-up of 1 Million Men and Women. In National Cacner Institute. Smoking and Tobacco Control Monograph 8. Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. National Cancer Institute. NIH Publication No 97-4213, 1997 pp 113-304.

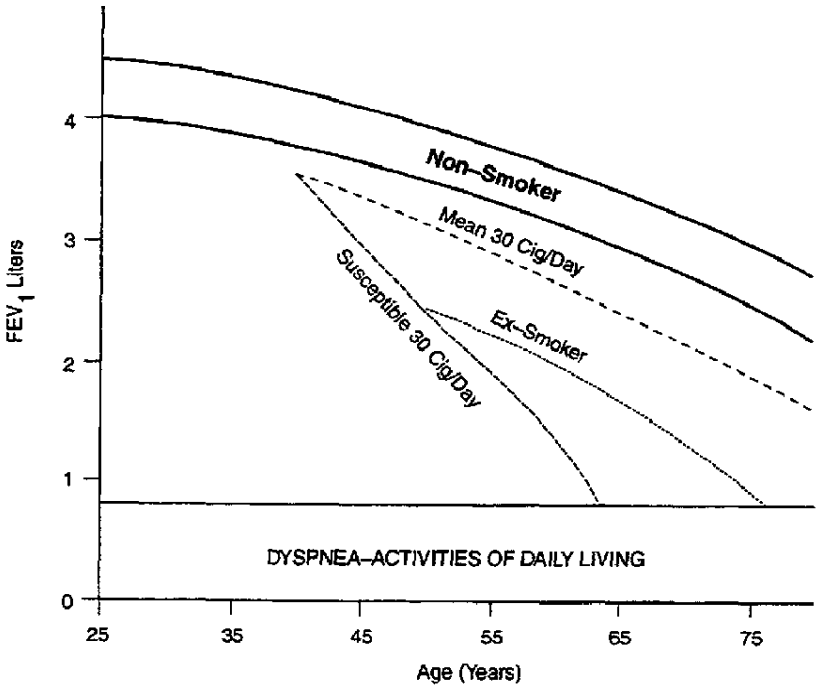
Figure 14-2 Pathogenesis of emphysema



NOTE: Scheme of smoking-induced pulmonary emphysema. Smoking recruits inflammatory cells to the lower respiratory system via stimulation of alveolar macrophages. Inflammatory cells release enzymes (peroxidase, myeloperoxidase) and oxygen free radicals that degrade the extracellular matrix of the respiratory tissues and interfere with normal repair mechanisms. Tobacco smoke also contains oxygen free radicals that, together with products released from inflammatory cells, inactivate protease inhibitors such as α_1-AT.

SOURCE: Reprinted with permission from Senior RM, Shapiro SD. Chronic obstructive lung disease: Epidemiology, pathophysiology, and pathogenesis. *In* Fishman, A. Pulmonary diseases and Disorder, 3rd ed. (1998) McGraw-Hill companies. Copyright (1998) by McGraw-Hill Companies.

Figure 14-1 FEV1



NOTE: Scheme showing loss of forced expiratory volume at 1 second (FEV_1) with age. Nonsmokers lose lung function with age, about 30 ml per year. Smokers of 30 cigarettes/day have a greater rate of loss (dashed line). A small proportion of smokers (10–15%) have a steeper rate of decline, about 60 ml per year (dot and dashed line). This susceptible group of smokers reaches an FEV_1 of 0.8 liter (the level at which shortness of breath occurs on activities of daily living) at approximately 60–70 years of age. If a susceptible smoker stops smoking at age 50, the rate of decline follows that of the nonsmoker (dotted line), showing that smoking cessation may prolong onset of symptoms.

SOURCE: Reprinted with permission from Piquette CA, Rennard SI, Snider GL: Chronic bronchitis and emphysema. *In* Murray, J.F., Nadel, J.A. Textbook of Respiratory Medicine 3rd ed. W.B. Saunders Company: Philadelphia. 2000 Copyright (2000) by W.B. Saunders Company.

TABLE 14-3. Relationships between cotinine levels in asthmatic children exposed to environmental tobacco smoke

Author and Year	Study Type and Sample Size	Asthma Population	Cotinine	Asthma	Finding
Group A – Association of High cotinine levels with asthma					
Willers et al. 1991	Case-control 49/77	3-15 yr. Old, clinic	Urinary	Self-reporting symptoms	Cotinine levels greater in cases than controls ($p<0.005$)
Ehrlich et al. 1992	Case-control 72/121	3-14 yr. Olds, Er* and clinic	Urinary, grouped <30 ng/ml or >30 ng/ml	Clinical Exam	Cases had higher cotinine levels than control (OR*=1.9, 95% CI* 1.0- 3.3)
Chang et al., 2000	Case-control 165/106	2 mo. – 16 yr., ER	Salivary	Clinical Exam	No difference in cotinine levels between case and control groups
Group B – Dose-effect relationship between cotinine and asthma severity					
Chilmonczyk et al., 1993	Case control 199/199	8 mo. – 13 yr., clinic	Urinary, grouped, <10, 10-39, >39 ng/ml	Asthma exacerbations; lung function	Monotonic relationship for ↑ exacerbations and ↓ function
Rylander et al., 1995	Case-control 199/351	4 mo. to 4 yr., hospital	Urinary	Clinical Exam	Risk of wheezing increased with cotinine concentration
Ehrlich et al., 1996	Case-control 368/294	7-9 yr. Old; heavy household smokers	Urinary	Self-reported symptoms	Positive exposure-response relationship for asthma and cotinine by quartile ($p=0.02$)
Oddoze et al., 1991	Cross sectional 90	4-14 yr., clinic	Urinary	Bronchial responsiveness	Bronchial responsiveness correlated with cotinine level ($p<0.03$)

*Abbreviations: ER, emergency room; OR, odds ratio; CI, confidence interval

An alternative is to proceed with interventional trials based on current knowledge if there are uncertainties about the added value of dose–effect data or untested biomarkers to study design. As an example, an intervention study of the effect of smoking reduction on COPD could be considered that is similar in design to the Lung Health Study, a large prospective trial of the effects of smoking cessation on rate of decline of FEV_1 in middle-aged smokers with mild COPD (Anthonisen et al., 1994). Another approach is to conduct a trial using a low-tar/moderate-nicotine product from a noncommercial source to avoid product endorsement issues. (A more detailed research agenda can be found in the next section.)

Design of population studies for harm reduction of major respiratory diseases is challenging because of uncertainties about effectiveness and long-term compliance with harm reduction interventions. Reducing the burden of tobacco-related respiratory diseases through harm reduction strategies should be a major priority of the nation's public health.

RESEARCH AGENDA

This section outlines a suggested research agenda for studying harm reduction due to cigarette smoking in respiratory diseases (i.e., COPD, asthma, respiratory infections).

Several specific suggestions for research design arise from this review. An interventional study of the effect of smoking reduction on COPD could be considered that is similar in design to the Lung Health Study, a large prospective trial of the effects of smoking cessation on rate of decline of FEV_1 in middle-aged smokers with mild COPD (Anthonisen et al., 1994). In a proposed smoking reduction trial, it might be possible to include an intervention group of smokers who are able to reduce their smoking spontaneously and maintain significant reductions for a long period using behavior intervention and/or nicotine replacement products. The goal would be to decrease the number of cigarettes per day to 8–10, a point below which it is very difficult to reduce the number of cigarettes smoked (Hughes, 2000). The primary end point could be the change in FEV_1 over 5 years, and secondary end points could be exhaled carbon monoxide concentration, serum cotinine level, survival, and comorbid smoking-related disorders. If successful, this study should be able to determine whether reduced smoking as measured by change in FEV_1 mitigates harm to the lungs. Potential weaknesses are the self-selection of subjects, the large number of subjects required, ethical issues regarding the nonintervention group, and a probable large dropout rate in the intervention group.

Another approach is to conduct a trial using a low-tar/moderate-nicotine product from a noncommercial source to avoid product endorsement issues. This study might be conducted in two phases. Phase I would be a controlled-exposure study in human smokers to compare the effects of the low-tar/moderate-nicotine product versus a reference cigarette on inflammatory changes in the lower respiratory tract, similar to the observations of Rennard et al. (Rennard, 2000). The objective of Phase I would be to determine if inflammation is reduced by exposure to the low-tar/moderate-nicotine product. If so, a Phase II intervention trial would compare the low-tar/moderate nicotine product to reference cigarettes in cohorts of current smokers. The objectives and design of the Phase II trial would be similar to that described above for intervention using behavioral modification or NRT. Potential advantages of this trial are that the low-tar/moderate-nicotine product, if it reduces harm, could be used as a reference product for future regulation of marketed products. Uncertainties related to such a study include inference from results of short-term controlled exposures to longer-term studies, controlling use of the intervention product, and the large effort that would be needed to complete the study.

sus the control group (Greenberg et al., 1994). However, there was uncertainty about the effectiveness of the intervention since the mean cotinine levels did not differ between study groups despite a reduction in smoking levels in the intervention group.

SUMMARY AND CONCLUSIONS

In evaluating the use of potential reduced-exposure products (PREPs) in tobacco-related lung disease, three major nonneoplastic respiratory diseases linked to cigarette smoking should be considered: COPD, asthma, and respiratory infections. Respiratory diseases are major tobacco-related illnesses, and there is a clear need to mitigate the harmful effects of exposure to both mainstream and secondary tobacco smoke. It is plausible that decreasing smoking will reduce the severity of chronic lung diseases and the incidence of respiratory infections, but there is no adequate scientific evidence to support this conclusion because the effects of reduced smoking on harm reduction have not been extensively studied.

Important considerations are determining dose–effect relationships and use of respiratory disease biomarkers. Rational design of studies of harm reduction would rely on dose–effect data, but such data for respiratory diseases are limited and of uncertain quality. High-quality dose–effect data are required for adequate study design, and such data should be generated. Rational study design would also incorporate biomarkers of disease, and the testing of current and new biomarkers might be done concurrently in the populations studied for dose–effects. The Cancer Prevention Studies I and II, large-scale prospective studies, however, do suggest a linear dose–effect relationship between number of cigarettes smoked per day and mortality rates from COPD, indicating that decreasing the amount of cigarettes smoked may lead to fewer deaths from COPD.

There are currently no specific biomarkers of respiratory disease due to smoking tobacco products. No unique molecular or genetic defect specific for tobacco-related respiratory disease has been identified. The processes involved, such as inflammation and increased levels of oxidants, are not unique to tobacco-related respiratory diseases. Identifying unique biomarkers is further confounded by the heterogeneous nature of these diseases, the complex mixture of tobacco smoke, and the range of individual susceptibilities to the harmful effects of tobacco smoke among users. The most widely used markers of tobacco-related respiratory diseases in population studies are symptom questionnaires and pulmonary function testing. These have well-known limitations of specificity and sensitivity, particularly for detecting the early effects of tobacco smoke on the lungs (U.S. DHHS, 1989). Subtle effects of tobacco smoke exposure on the lung can be detected by sampling fluid in the lower respiratory tract via a bronchoscope inserted into the airways, but the significance of these changes to clinically important pulmonary disease has not been established. Newer approaches such as sampling the subjects' urine (Pratico et al., 1998) or exhaled gas (Paolo et al., 2000; Ichinose et al., 2000) for metabolic products due to tissue injury have the advantage of noninvasive sampling but must be validated. Clearly, the greatest obstacle for developing a specific biomarker is the lack of fundamental information on mechanisms by which exposure to tobacco smoke causes specific respiratory diseases.

The availability of dose–effect data and validated biomarkers may improve the quality of, and provide greater confidence in, the results of contemplated intervention studies. However, the time frame for generating dose–effect data and testing biomarkers is uncertain, and it is unclear whether inclusion of dose–effect considerations and biomarkers will improve the quality of clinical trials of harm reduction in respiratory diseases.

All 14 studies in this group found an increased risk associated with parental smoking. The results of the community and hospital studies were broadly consistent, with only one study reporting a reduced risk among children of smokers. The pooled odds ratios were 1.6 (95% CI = 1.4, 1.9) for smoking by either parent and 1.7 (95% CI = 1.6, 1.9) for maternal smoking. The associations for parental smoking were robust to adjustments for confounding factors. In general, the evidence was more convincing for an association with smoking by the mother only than by the father only, probably related to a greater degree of exposure to the mother. Twelve cohort studies presented evidence for dose–response within smoking families, either to the number of smokers or to the amount smoked in the household. A statistically significant dose–response relationship was found in 10 of the 13 cohort studies (Cook and Strachan, 1997; Cook et al., 1998). In two case-control studies (Reese et al., 1992; Rylander et al., 1995), urinary cotinine levels were measured, but in neither study was it possible to determine if the cotinine levels were related to the risk of respiratory illnesses. The effect of paternal smoking on respiratory illnesses was most marked in the first year of life (Colley et al., 1974; Fergusson et al., 1981; Fergusson and Horwood, 1985), but the effects of maternal smoking on hospital admissions for respiratory infections were similar at all ages up to 5 years (Taylor and Wadsworth, 1987). There appears to be no increased risk of respiratory infections in susceptible subgroups (i.e., history of parental allergy, prematurity, low birthweight) (Burr et al., 1989; Lucas et al., 1990; Ehrlich et al., 1996; Chen, 1994).

Although the studies are generally consistent with an association between parental smoking and lower respiratory tract infections in children, the summary odds ratios derived from the pooled studies should be interpreted with caution. Difficulties with the pooled analysis include the process by which the variables were selected, the different types of data collection and analytical approaches applied to each study, and the inconsistent methods used to account for confounding effects. In addition, the precise nature of the specific diagnosis of lower respiratory tract infections and overlap with childhood asthma are important barriers to the analysis. The quality and sizes of the populations in these studies varied considerably, possibly introducing certain biases. Despite these limitations, it is reasonable to conclude that there is a causal relationship between parental smoking and acute lower respiratory illnesses at least during the first 2 years of life.

Latency

The effect of active smoking and smoking cessation on age-adjusted mortality from infectious diseases was examined in the American Cancer Society CPS-II study. Male former smoker of less than 15 cigarettes per day have mortality ratios after 10 years approaching unity, whereas former smokers of more than 21 cigarettes per day have mortality ratios near unity at 15 years. Female former smokers of any amount have mortality ratios from influenza and pneumonia approaching unity within 3–5 years. These results suggest that impaired host defenses are reversible after smoking cessation.

Review of Harm Reduction Strategies Applied to Respiratory Infections

One controlled intervention study has examined the effect of acute lower respiratory tract infection after an intervention designed to modify postnatal exposure to tobacco smoke (Greenberg et al., 1994). There was a reduced prevalence of lower respiratory symptoms among the intervention group of infants of smoking mothers whose education level was high school or less ver-

smoking and mortality from influenza and pneumonia has been studied in several cohort studies. In the American Cancer Society CPS-I, the standardized mortality ratio for deaths due to influenza and pneumonia for ever smokers compared to never smokers was 1.9–1.7 for males and 1.3 for females (Hammond, 1965). In the British Physician Study (Doll and Peto, 1976), there was a slight increase in risk for current smokers, and an dose–response relationship was noted by the amount smoked. Similar results were found in the U.S. Veterans Study (Rogot and Murray, 1980) and in a study of Swedish men (Carstensen et al., 1987).

Cigarette smoking is an independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults (Nuorti et al., 2000). A dose–response relation was found for invasive pneumococcal disease and number of cigarettes smoked daily, pack-years of smoking, and time since quitting. Thus, cigarette smoking increases the risk of certain respiratory diseases and predisposes to increased invasiveness of pneumococcal disease.

Smoking has been studied as a possible risk factor for tuberculosis. Although research has been sparse, it has been postulated that smokers are at increased risk of developing active pulmonary tuberculosis. A case-control study by Alcaide and associates (1996) found smoking to be linked to the development of pulmonary tuberculosis in infected subjects who were in close contact with a case of active pulmonary tuberculosis. The risk of active tuberculosis was increased by exposure to environmental tobacco smoke. The significance of the association remained after controlling for social and economic status, age, and gender, but it became not significant in those exposed only to passive smoking. A dose–response effect was also described in this study, although findings have been inconsistent in other studies. Children exposed to passive smoking were found to have increased risk of developing active pulmonary tuberculosis after having been infected (Altet et al., 1996). This association persisted after controlling for age and social and economic status. Although there are few studies, smoking has been linked to positive skin test conversions (Anderson et al., 1997). The mechanism postulated is that smoking decreases immune defenses and increases susceptibility to pulmonary tuberculosis (Plit et al., 1998).

Secondary Smoke Exposure

Compelling evidence exists for a causal relationship between parental smoking and lower respiratory infections (bronchiolitis, pneumonia) during childhood. Strachan and Cook (1998) have reviewed 40 published series on this topic, which included papers in previous reviews (U.S. DHHS, 1986, 1993; DiFranza and Lew, 1996). The studies sought to ascertain the relationship between lower respiratory illnesses and parental smoking in children less than 3 years old.

In one group, the occurrence of lower respiratory infections was based on data from a community or ambulatory care setting and included longitudinal studies, controlled trials, case-control studies, and retrospective prevalence surveys. The illnesses included unspecified lower respiratory illness, bronchitis, bronchiolitis, and pneumonia.

The most widely derived measures of effect related to either parent smoking (compared with neither parent) and the effect of maternal smoking (compared with father only or neither parent). Information was sought to determine whether there was a dose–response relationship by relating illness to the amount smoked by either parent. A second series of studies analyzed the association between hospital admissions for lower respiratory tract infections and parental smoking. Diagnoses included undifferentiated chest illness, bronchitis and/or pneumonia, wheezing illness, and bronchiolitis with or without confirmation of respiratory syncytial virus.

Pathogenesis

The respiratory tract in the normal host is effective in containing microbes present in the environment. The airways below the level of the major bronchi are mostly sterile, and special situations predispose to respiratory tract infections. These include the introduction of a new species into the environment, such as an antigenic shift in influenza virus. A second situation involves an overwhelming inoculum of organisms, such as exposure to contaminated ventilatory equipment. A third situation results from impairment of part of the host respiratory defense apparatus or systemic immune response. The major components of the respiratory host defenses are the mechanical barriers of the upper respiratory tract, locally secreted immunoglobulins, lymphoid structures of the bronchi, phagocytic macrophages, and a number of immune and nonimmune substances that line the alveolar surfaces (Reynolds, 1997). Components of the host defense system are specially designed to deal with large particulates (3–10 μm) in the upper respiratory tract and small particles (0.5–<3 μm) that may reach alveoli. If inflammation occurs in the alveoli, various systemic immune components can enter the airspaces by leakage through the alveolar surface. If local host defenses are insufficient, the host can recruit additional phagocytic cells such as polymorphonuclear leukocytes (PMNs) and create a local inflammatory response. The creation of an inflammatory response considerably increases the repertoire of systemic immune responses that can be recruited to contain the spread of microbes (Delves and Roitt, 2000). If the infection is successfully contained, inflammation is terminated and lung tissue is restored to its normal state. If it is not contained, inflammation can spread locally, leading to pneumonia. If severe, the local responses may produce permanent damage such as scarring to lung structure.

The effects of exposure to cigarette smoke on immune and inflammatory responses have been studied extensively in humans (Holt, 1987; Johnson et al., 1990). Alteration of immune and inflammatory processes by cigarette smoke are also relevant to asthma and COPD. Both acute exposure and chronic exposure to cigarette smoke alter the responsiveness of the immune system. The magnitude and direction of the alteration depend on the quantity and duration of exposure and the particular immune functions being studied. In general, low concentrations and short exposures enhance immune response, whereas high concentrations and long-term exposures suppress the responsiveness of the immune system. Many of the effects appear reversible within several weeks or months following cessation of exposure even after long periods (years) of exposure. The pulmonary tissues directly in contact with the smoke and the associated regional lymphatics are more affected than the peripheral immune system. Smokers have serum immunoglobulin levels that are 10–20% lower than those of nonsmokers (Holt, 1987; Mili et al., 1991). In addition to impairment of the peripheral immune system, smoking impairs mucociliary clearance, enhances bacterial adherence to respiratory epithelium, and disrupts respiratory epithelium (Green and Carolin, 1967; Fainstein and Musher, 1979; Raman et al., 1983; Dye and Adler, 1994). These altered functions may explain the higher rates of nasopharyngeal colonization with meningococcus among active and passive smokers compared to nonsmokers (Stuart et al., 1989).

Mainstream Smoke Exposure

Cigarette smoking is associated with increased susceptibility to certain types of respiratory infections (Haynes et al., 1966; Parnell et al., 1966; Peters and Ferris, 1967; Finklea et al., 1969; Aronson et al., 1982; Kark et al., 1982; Stanwell-Smith et al., 1994; Imrey et al., 1996; Straus et al., 1996; Fischer et al., 1997; Nuorti et al., 2000). The dose–response relationship between

Review of Harm Reduction Strategies Applied to Asthma

Several studies have examined the effect of reducing tobacco smoke exposure on wheezing symptoms. In one study (O'Connell and Logan, 1974), parents of a subpopulation of children in whom ETS exposure was considered a "significant factor" were given antismoking advice and followed for 6–24 months. Symptoms improved in 90% of children whose parents stopped smoking and in 27% of children who remained exposed to passive smoking. These results are difficult to interpret because this is an uncontrolled trial. In a second study (Murray and Morrison, 1989), severity of asthma was scored in a group of children with the diagnosis of asthma whose mothers smoked. When the group was scored 3 years later, there was a highly significant decline in lung function in children of mothers who continued to smoke but an improvement in lung function of children whose mothers no longer smoked. This reduction was attributed to an alteration of maternal smoking habits, but this explanation is based on anecdotal evidence. A randomized, controlled trial to investigate whether brief intervention by advising parents about the impact of passive smoking would reduce salivary cotinine levels in asthmatic children was found to be ineffective (Irvine, 1999). A study of the relationship between modifications of parental smoking behavior and nicotine exposure found that smoking outside the home was associated with lower urinary cotinine levels only when the parent was the only smoker in the house (Winkelstein et al., 1997). These intervention studies lack assessment of confounders and require a more rigorous design. Intervention studies, utilizing dose–response relationships between asthma severity and levels of environmental tobacco smoke, represent a future strategy for evaluating harm reduction from ETS in asthmatic children.

RESPIRATORY INFECTIONS

Definition and Epidemiology

Viral rhinitis, tracheobronchitis, and bacterial bronchitis are acute infections of the epithelium of the upper respiratory tract. According to the 1997 National Center for Health Statistics survey (NCHS, 1999), upper respiratory infections are the most common medical reason for school or work absenteeism in the United States. These infections can occur in healthy people during epidemics. Immunocompromised patients are at special risk of developing pneumonia and tuberculosis. More serious infections of the lower respiratory tract such as pneumonia are less common in normal hosts. In elderly hospitalized individuals, nosocomial pneumonia is a major health problem and risk to life. Tuberculosis is a disease of the lower respiratory tract present predominately in socially and economically disadvantaged populations and in immunosuppressed patients in the United States, but it is a major health problem worldwide.

Respiratory tract infections and pneumonia are particularly important causes of death in the United States. In 1997, the combined cause-of-death category "pneumonia and influenza" ranked sixth among the leading causes of death (MMWR, 1999). The age-adjusted mortality rate oforpneumonia and influenza was 12.9 deaths per 100,000 population. During the interval from 1977 to 1997, the death rate from pneumonia and influenza increased 15.2% (MMWR, 1999). The number of deaths in the United States in 1990–1994 due to respiratory infections that were attributed to cigarette smoking was estimated to be 8,000 per year (Table 14-2). Pneumonia and influenza are particularly important in the elderly, and the death rate reaches 20% in community-acquired pneumonia (Feldman, 1999; Fine et al., 1996). During 1997, in children aged 1–4 years, the combined category pneumonia–influenza was the sixth leading cause of death, and it was the seventh leading cause of death in children 5–14 years of age (NCHS, 1999).

pulmonary function studies comparing children exposed to environmental tobacco smoke and children who are unexposed. The incidence of wheezing illnesses in children whose parents smoke is greatest in early life, whereas the incidence of asthma during school years in less strongly affected by parental smoking. This may be due to a stronger influence of viral-associated wheezing in early childhood or less exposure to maternal smoke among older children.

The results of effects on spirometric indices of passive smoking have been reviewed (Cook et al., 1998; Cook and Strachan, 1999). These analyses concluded that passive smoking is associated with a small but significant reduction in FEV_1 and other spirometric indices in school-age children without asthma. For example, the large Six Cities Study showed a very small but significant effect of maternal smoking on lung growth (minus 3.8 ml per year for FEV_1) (Tager et al., 1983). Such subtle reductions are unlikely to impact the rates of development of chronic obstruction in airflow unless data emerge demonstrating that children exposed in early life have more rapid decline of lung function. Unfortunately, none of the longitudinal studies have looked at changes in lung function in relation to change in maternal smoking behavior. Therefore, it is unknown whether their effects are reversible. Similarly, a study in infants demonstrated that a family history of parental smoking contributes to airway hyperresponsiveness at an early age (Young et al., 1991). Whether these normal, healthy infants with airway hyperesponsiveness develop asthma as adults is not known.

An important issue in evaluating potential strategies for reducing harm from environmental cigarette smoke among asthmatic children in smoking households is to assess the relationship between biomarkers of cigarette smoke exposure and severity of asthma. If a dose–effect relationship exits, these data might indicate the approximate extent of reduction in exposure that may be expected to reduce the severity of asthma in children residing with smokers. Several studies have examined the dose–response relationship in asthmatic children using cross-sectional or case-control designs (Table 14-3). Asthma was assessed by self-reporting, physical examination, or lung function studies, and cotinine was measured in urine or saliva. Two general types of analyses were done: (1) associations of mean levels of cotinine in asthmatic or control groups (Group A) and (2) relationships between cotinine levels and asthma severity (Group B). Two studies (Willers et al., 1991; Ehrlich et al., 1992) found higher levels of cotinine in urine of asthmatics than controls, and one study found that cotinine levels in saliva were no different in asthmatics and control subjects (Chang et al., 2000). Four studies showed a relationship between urinary cotinine levels and the severity of asthma (Chilmonczyk et al., 1993; Rylander et al., 1995; Ehrlich et al., 1996; Oddoze et al., 1999) (see Table 14-3).

There are methodological problems with these studies, however, since most have not controlled for confounding factors such as respiratory illnesses or exposure to house mite antigen. It is possible that children of parents who smoke are more likely to become allergic or to have respiratory infections. Moreover, the effects are applicable only to some age groups or some symptoms of asthma, leading to inconsistencies in the reported results. Finally, the clinical significance of the small differences in lung function or symptoms is unknown. Therefore, there is uncertainty about whether a dose–response relationship exists between cigarette smoke exposure as measured by cotinine levels and severity of asthma, and this subject requires more study before harm reduction studies can be planned.

smoking. Their investigators also found a dose–response relationship with the amount smoked and the number of parents smoking. Greer and associates (1993) studied a large, nonsmoking population over a 10-year period to examine the association between workplace exposure to environmental tobacco smoke and the development of asthma. After controlling for confounding factors, workplace ETS exposure was a significant risk for asthma (relative risk [RR] = 1.5, 95% CI = 1.2, 1.8). In another study of more than 4000 never-smoking adults, Leuenberger and associates (1994) found exposure to environmental tobacco smoke at home or work was associated with physician-diagnosed asthma (OR = 1.4, 95% CI = 1.0, 1.9).

Several studies have examined the role of environmental tobacco smoke as a factor for asthma in adults. There are limitations of present epidemiological studies including potential biases in both subject selection and misclassification of exposure and differing designs. The effects of environmental tobacco smoke on pulmonary function in otherwise healthy adults are likely to be small and unlikely to result in clinically significant chronic respiratory disease (California Environmental Protection Agency, 1997). Although the results tend to indicate potential effects of environmental tobacco smoke as a cause of asthma in adults, the present epidemiological data are limited and have to be interpreted cautiously.

The results of published reports on the effects of ETS exposure on respiratory symptoms and lung function in adults have been summarized by Tredaniel and associates (1994) and Coultas (1998). Six observational studies in patients and six experimental studies of patients with asthma are reviewed. In general, these studies report that environmental tobacco smoke worsens respiratory symptoms and lung function among adult asthmatics. There are no published intervention trials in adults examining whether decreasing exposure reduces asthma symptoms or impairment of lung function.

A recent review evaluated the quality of the studies of the relation of environmental tobacco smoke as an exacerbating factor for asthma in adults (Weiss et al., 1999). Although exposure of adult asthmatics to environmental tobacco smoke was associated with increased symptoms of asthma, these studies are subject to recall and information bias, and no firm conclusions can be made. On the other hand, a number of controlled exposure studies have examined the effect of exposure to environmental smoke in healthy adult volunteers and subjects with asthma (Weiss et al., 1999). In general, the experimental studies show that brief exposure to ETS produces symptoms such as eye and nasopharyngeal irritation with less consistent responses in terms of lung function. Airway hyperreactivity after environmental smoke exposure was assessed by bronchoprovocation tests using methacholine. The majority of these studies failed to document an effect on ventilatory function or measures of airway responsiveness. In general, studies evaluating acute exposure of adult asthmatics to environmental tobacco smoke have generated conflicting data, yet there is evidence that some asthmatics and groups of asthmatics do respond to ETS levels that do not elicit responses in healthy volunteers. However, because of the limited number of studies and potential problems in their design, definitive conclusions cannot be drawn at this time.

Children

The relationship between environmental tobacco smoke and asthma, lung function, and respiratory symptoms in childhood has been reviewed (NRC, 1986; U.S. DHHS, 1986; Strachan and Cook, 1998; Cook and Strachan, 1997; Cook et al., 1998). Most of the studies support the notion that small but significant differences can be detected in respiratory symptom prevalence and

upon active cigarette exposure. In a cross-sectional study of 225 adult asthmatics, current smokers had a higher asthma symptom scores than nonsmokers when adjusted for age, gender, and physician visits (Althuis et al., 1999). However, there are methodological issues that might obscure the associations between active smoking and asthma in cross-sectional studies. One form of selection bias, referred to as the healthy smoker effect (Weiss et al., 1999), refers to self-selection of subjects with less mild asthma as active smokers compared to those who remain smokers. The probability of an asthmatic becoming an active smoker may be less in individuals have a greater airway hyperreactivity or who become more symptomatic when they smoke. Similarily, adults who had childhood asthma may be more likely to remain nonsmokers than those who did not have asthma in childhood. Thus, cross-sectional studies of smoking and asthma have limitations of interpretation. Nevertheless, observational studies show that asthmatics who are unable to cease smoking have more serious problems with control of asthma and have more frequent hospital admissions than nonsmoking asthmatics (Abramson et al., 1995; Floreani and Rennard, 1999).

Since the 1960's, it has been suggested that airways hyperresponsiveness and atopy are risk factors for the development of COPD, the so-called Dutch hypothesis (Orie et al., 1961). Data from several longitudinal studies now clearly show that airways hyperreactivity is a susceptibility factor for accelerated decline of lung function in active cigarette smokers compared to smokers without airways hyperreactivity (Tashkin et al., 1996; Rijcken et al., 1995; Tracey et al., 1995; O'Connor et al., 1995, Frew et al., 1992). Data from the Lung Health Study, a five-year prospective study of subjects with mild COPD, showed that responsiveness to methocholine at the initiation of the study was a strong predictor of change in FEV1 in continuing smokers even after controlling for baseline lung function, number of cigarettes smoked, and demographic variables (Tashkin et al., 1996). Moreover, airway reactivity appeared to be a more important determinant of subsequent lung function decline then baseline lung function. In addition, the magnitude of the decline in FEV1 increased with greater levels of airways hyperreactivity. The design of the study did not permit the distinction of whether the risk factor for progression of COPD was airway hyperreactivity itself or an underlying mechanism of reactivity such as inflammation. The finding that the effect of reactivity on lung function decline was greatest in continuing smokers compared to subjects who quit smoking suggests that the effect at least partially due to progressive airway damage induced by smoking. Since subjects who reduced smoking were not analyzed, there is insufficient information to determine whether decreasing the number of cigarettes smoked leads to less airways hyperreactivity.

Environmental Tobacco Smoke Exposure

Adults

The three major reviews of the health effects of passive smoking published between 1986 and 1992 cited no literature directly examining the association between passive smoking and asthma in adults (NRC, 1986; U.S. DHHS, 1986). Coultas (1998) reviewed studies on this topic from 1992 to 1998 and classified them as etiological studies (the association between passive smoking and the diagnosis of asthma) and morbidity studies (the role of passive smoking in causing symptoms or worsening lung function in patients with asthma). Among the papers reviewed was that of Hu and coworkers (1997) who observed in young adults that physician-diagnosed asthma was associated with parental smoking. The odds ratio was 1.6 (95% confidence interval [CI] = 1.1, 2.3) for maternal smoking and 1.3 (95% CI = 0.9, 1.8) for paternal

associated increase in the existing airways hyperreactivity to a variety of stimuli" (NIH, 1997). There is no standardized method for measuring asthma, and the lack of standardization has hampered the investigation of asthma by making it difficult to compare results of different studies (Woolcock, 1994).

Asthma is an extremely common disorder in the United States, with approximately 10–15% of boys (Sly, 2000), 7–10% of girls (Sly, 2000), and 5% of adults having signs and symptoms consistent with asthma (Drazen, 2000). Asthma has its origins primarily in childhood, with 50% of all asthma diagnosed by 3 years of age and 80% by 6 years of age (Yunginger et al., 1992), although asthma may develop at any time throughout life. The worldwide incidence of asthma has increased more than 30% since the 1970s (Weiss et al., 1993). A disproportional fraction of these cases have occurred among socioeconomically disadvantaged urban dwellers. The reason for the increased incidence of asthma is not known. In the United States, the overall age-adjusted prevalence of asthma increased 54% from 1980 to 1993–1994 (from 31 to 54 per 1,000 population) (NCHS, 1999).

Pathogenesis

The factors that influence the pathogenesis of asthma include atopy (production of abnormal amounts of immunoglobulin E [IgE]), early respiratory illness (before age 2), and parental history of atopy (Woolcock, 1994). Allergens act as triggers of asthma attacks and provoke inflammation of the airways. Other triggers include exercise and air pollutants such as ozone and sulfur dioxide (Woolcock, 1994). Inflammation of the airways with lymphocytes, mast cells, and eosinophils and production of certain interleukins by these cells creates an environment that promotes the production of IgE. The links between infiltration of cells and the pathobiologic processes that account for episodic airway narrowing have not been clearly delineated. The constriction of airway smooth-muscle cells due to the local release of bioactive mediators or neurotransmitters is a widely accepted explanation for acute constriction of the airways, but thickening of airway epithelium and the presence of liquid in the lumen may also contribute. The consequences of airway obstruction are decreased flow rates throughout expiration. As the asthma attack resolves, airway narrowing reverses and flow rates return toward normal. These physiological and pathological changes account for intermittent symptoms of shortness of breath, coughing, and wheezing (Drazen, 2000).

Mainstream Smoke Exposure

Asthmatics have extreme sensitivity of the airways to chemical, physical, and pharmacological stimuli, which can cause pronounced airflow limitation (Drazen, 2000). Cigarette smoke is a complex mixture of irritant compounds. Smoking can potentially lead to amplification of the airway inflammation already present in asthmatics by a number of mechanisms including recruitment of inflammatory cells, enhancement of some cellular function, and release of proinflammatory mediators (Floreani and Rennard, 1999). For example, cigarette smoking stimulates production of cysteinyl leukotrienes (Fauler and Frolich, 1997), a class of mediators that is increased in asthmatics, causes rapid proliferation of cells in small airways (Sekhon et al., 1994). In addition to inflammation, cigarette smoking is associated with increased airway wall remodeling (U.S. DHHS, 1990), a change asociated with chronic asthma. Physiological studies have shown that direct cigarette smoking causes acute bronchoconstriction in subjects with asthma (Nadel and Comroe, 1961). Many patients with asthma report worsening respiratory symptoms

airways was scored by directly visualizing the degree of erythema and edema though the bronchoscope.

Reduced smoking by approximately 50% (measured by self-reporting and exhaled CO) was achieved by the use of nicotine medication (Rennard et al., 1990). The amount of visible inflammation decreased but remained greater than that of nonsmokers. In lavage fluid, the number of inflammatory cells (particularly the pigment-laden macrophages and neutrophils) and the amount of elastase complexed to its α_1-antiproteinase inhibitor decreased after smoking reduction. These results show that reducing smoking from two packs to one pack per day produces a significant decrease in lung inflammation within 2 to 3 months. Whether the reduced inflammation results in less risk of developing COPD remains to be determined.

A second study examined the effect of switching to low tar and nicotine cigarettes (Rennard, 2000; ECLIPSE, 2000). This study differed from the nicotine replacement study in several ways: the subjects had moderate to heavy cigarette smoking (approximately 30 cigarettes per day) at enrollment, subjects chewed either nicotine gum (2 or 4 mg) or a placebo gum, and the duration of the study was 6 months. The groups that used NRT reduced their cigarette consumption (measured by self-reporting and exhaled CO). However, the group that used the low tar and nicotine cigarettes did not reduce smoking because they changed their smoking strategy to compensate. The results showed no reduction in the inflammation score in the group that used low tar and nicotine cigarettes, which was attributed to altered smoking strategy.

The study using heated tobacco (Eclipse™) was similar in design to the reports cited above and involved 12 smokers studied after a 3-month intervention. Exhaled CO was used to monitor cigarette use. Although one-third of the study group smoked conventional cigarettes, the number of conventional cigarettes used was small (97% of all products consumed were Eclipse™). In Eclipse™ users, inflammation scores and number of recovered alveolar macrophages decreased after intervention as did the density of goblet cells (an index of the mucous secreting cells) on bronchial biopsies. (Results of neutrophil counts were confounded by outliers in the control group.) After 3 months of Eclipse™, inflammation scores and goblet cells density remained above levels found in nonsmoking controls. The small number of patients and control subjects limits interpretation of this study.

In summary, asymptomatic smokers clearly have inflammation in their lower respiratory tract, and this inflammation is likely to be involved in the pathogenesis of COPD. The major conclusion of Rennard's (2000; ECLIPSE., 2000) studies is that smoking reduction has measurable effects on inflammation. It is plausible that reducing inflammation by reduced exposure to cigarettes will mitigate the development of COPD. However, the hypothesis that reduced smoking will lead to less severe COPD needs considerably more study using prospective intervention trials in persons susceptible to developing COPD.

ASTHMA

Definition and Epidemiology

Asthma is defined as a "chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an

primarily to test whether reducing smoking results in benefit as measured by less decline in lung function, but rather were designed to study the effect of cessation. Although they suggest that reducing smoking (at least in younger subjects) may slow the rate of decline in function, more rigorously designed prospective studies are needed to determine whether reducing smoking results in less harm to the lungs.

Decreasing Smoking Slows Decline in Lung Function

Numerous cross-sectional studies show that the level of smoking is a strong determinate of decline in lung function (U.S. DHHS, 1984, 1989). Multiple regression and analysis has been applied to these cross-sectional studies to determine the quantitative relationships between the rate of decline in FEV_1 and pack-years of cigarettes smoked (Burrows et al., 1977a; Dockery et al., 1988). In one study of over 8,000 men and women from U.S. cities (Dockery et al., 1988), it was estimated that the average male smoker lost 7.4 ml of FEV_1 for every pack-year of cigarettes smoked and that women lose 4.4 ml of FEV_1 in the population was skewed toward lower values for the smokers compared to the nonsmokers. This suggests that the loss in FEV_1 was relatively larger in smokers than nonsmokers. It is uncertain whether these data could be used to predict a slower rate of decline in lung function if a smoker reduced the number of cigarettes smoked over a prolonged period of time. There are several uncertainties about using studies of longitudinal change in lung function to predict slowing of lung function after reducing smoking. For example, the observations were made over a limited span of the natural history of COPD and it is unclear whether the measured changes in reduced FEV_1. Function of pack-years smoked remains constant throughout the natural history of the disease. It is possible, for instance, that a more rapid decline in lung function takes place after an event such as an infection or that the rate of decline accelerates with age. Individual factors that contribute to the rate of decline of lung function are poorly understood and also influence progression of disease. Because of uncertainties about the natural history of COPD, it is not possible to use longitudinal studies of decline in lung function as a function of pack-years smoked to estimate the reduction in harm in terms of decline in lung function from reducing cigarette smoking.

Effect of Short-Term Smoking Reduction on Lung Inflammation

The beneficial effect of short-term smoking reduction has been studied in current smokers using a technique that enables inflammation in the lower respiratory tract to be examined directly (Rennard et al., 1990; Rennard, 2000; ECLIPSE, 2000). In current cigarette smokers, three approaches to reduce smoking consumption were used: administration of nicotine medication, switching to a low tar and nicotine cigarette, and using Eclipse™ (R.J. Reynolds Tobacco Company), a product that results in less combustion of tobacco and potentially generates relatively less tar than nicotine. All studies used a similar approach. Heavy smokers (at least two packs per day) who had no clinical or physiological evidence of COPD were enrolled. During the reduced smoking period, cigarette smoke exposure was monitored by exhaled carbon monoxide (CO) concentration, serum cotinine level, and self-monitoring the number of cigarettes smoked. Lung inflammation was assessed before and 2–3 months after reduced smoking using bronchoalveolar lavage. Inflammatory cells and protective antiproteinase molecules were measured in the fluid sample, and results were compared to those from nonsmokers. The degree of inflammation of the

pants were moderate to heavy smokers (mean consumption, 31 cigarettes per day) who were motivated to quit smoking. They were randomized into three groups: (1) smoking intervention, (2) smoking intervention plus a brononchodilator, and (3) usual care. Smoking intervention was intensive and involved 12 group meetings in 10 weeks. Behavior modification was stressed, and nicotine replacement therapy (NRT) with nicotine gum was used aggressively. Those who ceased smoking entered a maintenance program. Relapses were treated individually. The main outcome was the rate of change in FEV_1 measured annually over 5 years. The cessation rate was among the highest reported in any trial. In the intervention group, 35% were abstinent 1 year and 22% were abstinent for 5 years (compared to 5% in the nonintervention group). The most important finding of this intent-to-treat analysis was that smoking cessation reduced the rate of decline of FEV_1. In a separate analysis of the study population, symptoms of cough and sputum production, but not dyspnea, improved after smoking cessation (Kanner et al., 1999). The administration of a bronchodilator (ipratropium bromide) resulted in a small improvement in FEV_1 at the onset of use. However, this effect reversed when the drug was discontinued at the end of the study. The major conclusion of the Lung Health Study was that an aggressive intervention program of smoking cessation reduces the age-related rate of decline in FEV_1 in middle-aged smokers with mild airway obstruction in the first year. After that time, however, the rate of lung function decline was not different in the two groups. These results provide a measure of the impact of aggressive smoking cessation compared with the usual care in reducing the harm of cigarette smoking.

A particularly important audience at which to target harm reduction is young smokers who want to quit. To determine how rapidly lung function returns to normal after smoking is stopped in this group of subjects, Ingram and O'Cain (1971) used sensitive tests of lung function (frequency dependence of compliance) in six asymptomatic young smokers. Within 8 weeks of smoking cessation, lung function had returned to normal in all subjects, suggesting that structural changes in the peripheral airways are reversible in these subjects after cessation of smoking.

There is a dearth of information on whether reducing cigarette smoking results in improvement in lung function. Two prospective studies in the 1970s and one in 1989 (Buist et al., 1976; McCarthy et al., 1976; Lange et al., 1989) examined the effect of reduced smoking over a 1 year period using volunteers with small-airway disease and either normal or mild reductions in FEV_1. Subjects who were able to reduce smoking consumption by 25% or more were considered to have reduced smoking. Tests of small-airway disease improved after smoking reduction, and in one study, FEV_1 showed slight improvement at 1 year (McCarthy et al., 1976). An observational study by Lange and colleagues in (1989) examined the effect of smoking habits on change in FEV_1 over a 5-year period in more than 7,000 Danish men and women. Among these were a sample of 189 subjects who were grouped as reducing smoking from more than 15 cigarettes per day to less than 15 cigarettes per day between intake and final examination. Regression analysis of change in age-adjusted FEV_1 over 5 years showed that smoking reduction resulted in a beneficial effect in younger subjects (less than 55 years old) but not in older subjects (more than 55 years old). In the younger group, the annual decline in FEV_1 unadjusted for age in women who were able to reduce smoking was 14 ml per year versus 30 ml per year in women who continued to smoke more than 15 cigarettes a day. For younger men who were able to cut back on smoking, the reduction was 17 ml per year compared to 42 ml per year in those who continued to smoke more than 15 cigarettes a day. Limitations of this study were that it was an observational study, smoking habits were based on self-reported data, and there were wide interindividual differences in the rate of decline of FEV_1. Further limitations of these studies are that they were not designed

rette smokers of developing COPD was assessed in 958 men and 1,159 women ages 25 to 64 years over a 10-year period (1967–1969 and retested in 1978–1979). At entry, patients were excluded who already had borderline or definite COPD. Data for the change in daily cigarette consumption were available from only one center. The odds ratio (OR) for developing COPD within 10 years predicted from the change in the number of cigarettes per day (number at follow-up minus number at entry into the study) was 1.7 for men and 2.4 for women. These results were interpreted as showing a benefit from stopping or reducing cigarette smoking. The limitations of this study are that it was not designed to show a change in mortality and morbidity for people who reduced smoking, that estimates are based only on survivors, and that it is a cross-sectional population study. Nevertheless, it does provide some evidence that reducing smoking might modify the risk of COPD.

The potential benefit to improving survival from COPD by reducing smoking can be analyzed from dose–response relationships between mortality and number of cigarettes smoked in a population. Such data are available from two large-scale prospective surveys of smoking and mortality among men and women in the United States sponsored by the American Cancer Society. The first survey of approximately 1 million people covered the period 1959 to 1972 and is referred to as Cancer Prevention Study I (CPS-I; Burns et al., 1997). The second survey was conducted from 1982 through 1986 on approximately 1.2 million people and is referred to as Cancer Prevention Study II (CPS-II; Thun et al., 1997). Methodological issues pertaining to calculations of risk-attributable mortality in these studies are discussed in the 1989 Surgeon General's report on reducing the health consequences of smoking (U.S. DHHS, 1989). Data are available from CPS-I that illustrate the relationship between cigarettes smoked per day and mortality rates from COPD among white male and female current smokers. Figure 14-3 shows data for two 15-year age groups (65–79 and 50–64 years). For both men and women age 65–79, the results show a monotonic increase in mortality rate from COPD as a function of number of cigarettes smoked per day, with higher rates in men than women. For men and women age 50–64, there is an apparent increase in mortality rate from COPD with number of cigarettes smoked per day, although the slopes are less steep than for the older group. These findings strongly suggest that increased cigarette smoking causes greater mortality due to COPD in current smokers.

One cannot infer from these results that reducing smoking will decrease mortality from COPD. However, the apparent by linear dose–response relationships suggest that decreasing the amount of cigarettes smoked may lead to fewer deaths from COPD. This may be particularly important to heavy smokers (more than 40 cigarettes per day). Caution is needed, however, in interpreting these results too simply. For example, it is unlikely that someone who smoked 40-plus cigarettes per day during adulthood will experience a substantial reduction in the risk of dying from COPD (e.g., comparable to that of a lifelong 20-cigarette per day smoker) if he or she were able to cut down on cigarette consumption. Only prospective studies of mortality in smokers who reduce their exposure to cigarettes will provide definitive answers to the question of how much mortality rates are decreased by reducing smoking.

Interventional Studies

A landmark study in smoking cessation in people at risk for developing symptomatic COPD is the Lung Health Study (Anthonisen et al., 1994). The study population consisted of 5,887 subjects from North America, 35 to 60 years old, who had presymptomatic COPD (no symptoms but abnormal lung function tests) and included a substantial fraction (37%) of women. Partici-

ternal smoking or differences in indoor environments (i.e., greater air mixing or exchange may decrease the concentration of environmental tobacco smoke). A recent study concluded that in utero exposure to maternal smoking is independently associated with decreased lung function in children of school age, especially for small-airway flows (Gilliland et al., 2000). Studies in neonates that excluded the effect of environmental tobacco smoke by measuring lung function after birth concluded that in utero exposure has an independent effect on reduced lung mechanics (Hanrahan et al., 1992; Stick et al., 1996). In a cross-sectional study by Milner et al. (1999), smoking was associated with a significant reduction in birthweight, but lung volume was not reduced when related to weight. Smoking was associated with a highly significant reduction in static compliance in boys and a small but significant reduction in respiratory conductance in girls. These authors concluded that smoking in pregnancy reduces static compliance in boys and conductance in girls although there was no evidence that maternal smoking adversely affected fetal development. Fetal lung hypoplasia has been produced in rats in a model of maternal cigarette smoke exposure (Collins et al., 1985). The weight of the evidence suggests that passive smoking contributes to COPD by causing a slight decrease in airway diameter that increases airway resistance.

Latency

There are limited data on the latency (Robbins et al., 1993) and dose–response (Dayal et al., 1994) between exposure to environmental tobacco smoke and the development of respiratory symptoms. Additional studies are needed, particularly of latency and dose–response relationships, to establish a causal relationship between passive smoking and COPD.

Review of Harm Reduction Strategies Applied to COPD

Impact of Smoking Reduction

It is plausible that reducing the number of cigarettes smoked per day would reduce disease risk. The presumption is that smoking causes morbidity and mortality in a dose-related manner. However, this presumption has never been formally tested (Hughes, 2000). One impediment to determining whether reducing smoking reduces risk is that a study would require a large number of subjects over a long time. Hughes (2000) estimated that 8,000 subjects would have to be followed for 8 years. A large study would be required since there are no adequate surrogate markers of disease. Since a large study of this type would delay implementation of harm reduction measures, one school of thought is that the benefits from smoking reduction can be assumed and we need not wait 8 years for the study to be completed (Hughes, 2000). Another school of thought argues that the decline in disease from smoking reduction may not be as great as presumed. This view is based on the following: (1) post hoc corrections for variables associated with smoking reduction may inflate mortality and morbidity among smokers, and (2) the expected reductions from "low-tar" cigarettes were not as great as expected (Hughes, 2000). It has been suggested that reducing smoking may undermine attempts at quitting, but based on limited evidence from three trials, Hughes (2000) concluded that there is no evidence to support this concern. It should be noted, however, that these results apply only to people who were self-motivated to reduce smoking, and the effects on quitting may not apply to the general population (Hughes, 2000).

There are data from retrospective cross-sectional, multicenter epidemiological studiessuggesting that reducing smoking reduces the risk of COPD (Higgins et al., 1984). The risk for ciga-

Coultas (1998) summarized the results of three studies (Leuenberger et al., 1994; Robbins et al., 1993; Dayal et al., 1994) published since the Environmental Protection Agency (EPA) report (US EPA, 1993) that concluded environmental tobacco smoke "may increase the frequency of respiratory symptoms in adults." Results of one population-based survey of self-reported COPD suggest that 3–5% of nonsmokers may be affected (Whittemore et al., 1995). The three published reports combined asthma and COPD. These studies all report similar findings that passive smoking is associated with chronic respiratory symptoms found in adults with COPD.

The second type of study examined declines in lung function and passive smoking in the development of COPD. Epidemiological studies have investigated the association between environmental tobacco smoke, respiratory diseases, and reduction in pulmonary function tests (Sherman, 1991; Tredaniel et al., 1994). It is controversial whether ETS exposure is associated with COPD. Some studies have reported greater reduction in pulmonary function in nonsmokers married to smokers and exposed to environmental tobacco smoke in the workplace (White and Froeb, 1980; Svendsen et al., 1987; Hole et al., 1989; Berglund et al., 1999; Leuenberger et al., 1994). However, most of the studies used sensitive indicators of lung function, and the physiological significance of small changes in lung function to COPD is not established. In addition, the effect of bias and confounding factors were not taken into account. No relation between passive smoking and reduced lung function in adults was found in two large cross-sectional studies (Comstock et al., 1981; Schottenfeld, 1984) and one longitudinal study (Jones et al., 1983). Thus, whether environmental tobacco smoke causes COPD in adults remains uncertain.

Current evidence suggests that the development of COPD in adults results from impaired lung development and growth in childhood, premature onset of declines in lung function, and/or accelerated decline in lung function (Kerstjens et al., 1997; Samet and Lange, 1996; Fletcher et al., 1976). Although passive smoking is a biologically plausible risk factor, the impact of passive smoking during adulthood on the development of COPD remains controversial. In a review of this topic, Tredaniel and associates (1994) summarized the results of 18 relevant publications. Eight reports found no effect of ETS exposure on lung function, and ten demonstrated small decrements. The authors pointed out the methodological limitations of these studies and raised questions about the relevance of small declines in lung function to the development of COPD. Coultas (1998) reviewed the results of three additional studies published since the Tredaniel et al. (1994) review and concluded that the results were inconsistent (two showing no effect and one showing an effect). In the study showing an effect, a large sample of never-smoking adults in Switzerland (Leuenberger et al., 1994), the association between increased symptoms of chronic bronchitis and environmental tobacco smoke was dose-related. The adjusted odds ratio of chronic bronchitis symptoms increased by years of exposure to environmental tobacco smoke, number of smokers to whom the subject was exposed, and workplace exposures (Leuenberger et al., 1994). An additional report published after Coultas' review concluded that environmental tobacco smoke in adults is associated with small defects in lung function (Carey et al., 1999).

Children

Exposure to passive smoking in childhood has been associated with reduced rate of growth of the lung as determined by change of ventilatory function with age in children exposed to environmental smoke compared to unexposed children (Berkey et al., 1986; Tager et al., 1979, 1983, 1987) (see Chapter 15). However, one cohort study failed to find any effect of maternal smoking on lung growth (Lebowitz and Holberg, 1988), possibly due to differences in the amount of ma-

Mainstream Smoke Exposure

The predominant risk factor for COPD is cigarette smoking, and it is estimated to account for 80–90% of the risk of developing COPD (U.S. DHHS, 1984). Cigarette smoking is associated with a lower FEV_1 in cross-sectional studies (Knudson et al., 1976; Burrows et al., 1977a; Dockery et al., 1988) and with an accelerated decline in FEV_1 in longitudinal studies (reviewed in Sherman, 1991). The lower FEV_1 in cross-sectional studies and accelerated rate of decline in FEV_1 exhibit a dose–response relationship. Both the duration of smoking and the amount smoked are significant predictors of lung function impairment (U.S. DHHS, 1989).

Individuals who smoke have age-adjusted death rates for COPD that are tenfold higher than those of "neversmokers" (U.S. DHHS, 1989). Mortality and morbidity rates for COPD are higher in pipe and cigar smokers than nonsmokers, although the rates are lower than in cigarette smokers. Factors predictive of COPD mortality include age at starting, current smoking status, and total pack-years. For reasons that are not known, only about 15% of smokers develop clinically significant COPD (Fletcher and Peto, 1977).

Data suggest that 10–15% of COPD cases are attributable to causes other than smoking, including occupational exposures to coal dust (Marine et al., 1988), grain dust (Zejda et al., 1993), air pollution (Bates, 1973; Rokaw et al., 1980; Buist and Vollmer, 1994), childhood respiratory infections (Burrows et al., 1977b; Shaheen et al., 1995), and airway hyperresponsiveness (Buist and Vollmer, 1994). Genetic factors that are independent of personal smoking history or environmental exposures also contribute to COPD (Khoury et al., 1985). These include α_1-antitrypsin deficiency, which accounts for less than 1% of cases of COPD (Snider, 1989). Additional genetic factors other than α_1-AT deficiency that appear to play a role in susceptibility to COPD have not been identified (Khoury et al., 1985).

Prospective population studies have shown an additive effect of air pollution on the decline in lung function in smokers (Tashkin et al., 1994; van der Lende et al., 1981). In a cohort study examining the additive effects of smoking and pollution on lung function decline, the mean adjusted decrement in FEV_1 attributable to smoking more than 24 cigarettes a day was 17.4 ml per year. An adjusted mean annual decrease of 8.9 ml per year was attributed to living in a moderately polluted environment compared to living in a clean environment (van der Lende et al., 1981). The conclusion of this study was that the decline in lung function attributable to smoking was twice as great when living in a polluted environment. In a prospective study of persons living in three communities with air pollution, a significant interaction between smoking more than 12 cigarettes a day and area of residence was found for mean decline of adjusted FEV_1 in males (Tashkin et al., 1994). These findings suggest an independent adverse effect of air pollution on decline of lung function in smokers.

Environmental Tobacco Smoke Exposure

Adults

Coultas (1998) has reviewed published reports of an association between ETS exposure and COPD. He classified three types of studies: two categories based on "indirect" measures of COPD (self-reports of symptoms of COPD; effects on lung function measurements) and a third category that used "direct" measures of COPD (mortality and hospitalizations). The studies focused on environmental tobacco smoke as a risk factor for developing COPD, not as factor that contributed to worsening of symptoms or lung function. In regard to self-reported outcomes,

Special tests of "small-airway" function were developed in the late 1960s and early 1970s to detect early changes in small airways (less than 2-mm diameter) that were are not detected on standard tests of pulmonary function (U.S. DHHS, 1984). When applied to prospective studies of populations, tests of small-airway function were not predictive for susceptible subjects who would progress to clinically significant airflow obstruction (U.S. DHHS, 1984). In subjects who exhibit accelerated deterioration of lung function (greater than 60 ml per year), this type of physiological testing was not predictive of the rate of development of clinically significant airway obstruction, probably because of the heterogeneous nature of COPD (Habib et al., 1987).

Mucous hypersecretion and infections have been postulated to play roles in the accelerated decline of pulmonary function in COPD. In adults, prospective studies have failed to show an association between acute chest infections and the rate of decline of FEV_1(Bates, 1973). Chronic mucous hypersecretion in earlier studies (Fletcher and Peto, 1977; Kauffmann et al., 1989; Higggins et al., 1982; Peto, et al., 1983) was not shown to be related to a decline in FEV_1 in COPD. More recent studies in larger samples of the general population have shown associations between chronic mucous hypersecretion and a decline in FEV_1(Lange at al., 1990; Sherman et al., 1992; Vestbo et al., 1996). In children, however, population studies suggest that childhood respiratory infection is a risk factor for the development of COPD in adults (Samet et al., 1983; Gold et al., 1989). The role of infections is unclear, but it is believed that bacterial colonization/infection stimulates inflammatory responses that cause local damage and progression of disease. In addition, infections impair host defenses and tissue repair, leading to further infection and perpetuating tissue injury (Murphy and Sethi, 1992).

Considerable evidence from human and laboratory studies suggest that oxidant–antioxidant imbalance in favor of oxidants occurs in COPD (Figure 14-2). The evidence is based on a large number of studies showing an increased oxidant burden and markers of oxidative stress in the airspaces, breath, blood, and urine of smokers and patients with COPD (Macnee and Rahman, 1999; Koyama and Geddes, 1998). Oxidants in patients with COPD are derived from oxygen free radicals in both the gas and tar phases of cigarette smoke (Pryor and Stone, 1993; Zang et al., 1995). Inflammation itself induces oxidant stress in the lungs of smokers as suggested by studies showing greater production of oxygen free radicals by leukocytes in smokers compared to nonsmokers (Morrison et al., 1999) and increased iron content, which promotes formation of free radicals in alveolar macrophages of smokers (Mateos et al., 1998). Pathological examination of the alveolar regions of smokers' lungs has shown increases in the number and percentage of leukocytes compared to nonsmokers (Hunninghake and Crystal, 1983). Recent studies have utilized analysis of exhaled gas in patients with COPD for gaseous products (i.e., reactive nitrogen species, ethane)(Paolo et al., 2000; Ichinose et al., 2000) and urinary products (isoprostane F_2-α-III) (Pratico et al., 1998) formed from oxidative stress. It is possible that measurement of products of oxidative stress in exhaled gas may be used as surrogate markers of inflammation in COPD. A possible mechanism whereby oxidants damage the lung is by inactivating the anti-elastase α_1-AT, thereby decreasing the capacity of α_1-antitrypsin to inhibit proteases (Carp et al., 1982; Johnson and Travis, 1979). This mechanism has been expanded to include proteinases other than neutrophil elastase and antiproteinases other than α_1-AT (Senior and Shapiro, 1998). Dietary deficiency of antioxidants has been proposed as a factor accounting for airflow limitation in elderly people (Dow et al., 1996), but dietary supplements of antioxidants have not been shown to modify clinical symptoms of COPD (Rautalahti et al., 1997; Macnee and Rahman, 1999; Traber et al., 2000).

Table 14-2 Relative Risk (RR) for Smoking-Attributable Mortality and Average Annual Smoking-Attributable Respiratory Disease Mortality (SAM) Among Current and Former Smokers, by Sex and Disease, United States, 1990–1994

	Men			Women			
Respiratory Disease	**Current Smokers RR**	**Former Smokers RR**	**SAM**	**Current Smokers RR**	**Former smokers RR**	**SAM**	**Total SAM**
Pneumonia, influenza	2.0	1.6	11,267	2.2	1.4	8,060	19,327
Bronchitis, Emphysema	9.7	8.8	9,642	10.5	7.0	6,475	16,116
Chronic airway obstruction	9.7	8.8	32,132	10.5	7.0	21,893	54,025
Other respiratory diseases	2.0	1.6	776	2.2	1.4	721	1,497
Total			**53,817**			**37,148**	**90,965**

SOURCE: Reprinted with modifications and permission from Novotny TE, Giovino GE. Tobacco Use. In Brownson, RE, Renington, PL, Davis, JR. Chronic Disease Epidemiology and Control 2nd ed. Washington, DC, American Public Health Association Press, 1998, pg. 117-148. Copyright 1998 by the American Public Health Association.

Pathogenesis

The role of inflammation and exposure to toxins in cigarette smoke is central to the pathogenesis of COPD (Aubry et al., 2000). There is considerable evidence to support the theory that pulmonary emphysema is caused by excessive exposure to elastolytic enzymes in relation to inhibitors of these enzymes, the "protease–antiprotease" theory (Barnes, 2000; Piquette et al., 2000). Cigarette smoke promotes injury to the lungs by increasing the proteolytic burden and compromising the antiproteolytic defenses leading to a breakdown in lung structure. The major antiproteolytic protein in the lower respiratory tract is α_1-antitrypsin (α_1-AT), although other proteinase inhibitors play a lesser role (Senior and Shapiro, 1998). In chronic bronchitis, an inflammatory airway response caused by chronic exposure to airborne toxins (cigarette smoke, dust, air pollutants) is the central pathogenic mechanism. (Barnes, 2000; Piquette et al., 2000). Inflammation leads to edema, cellular infiltration, fibrosis, smooth-muscle hypertrophy, and secretions that narrow the bronchioles.

Animal models of emphysema and chronic bronchitis have been used to study the pathophysiology of COPD (Shapiro, 2000; Drazen et al., 1999), including the contribution of tobacco smoke (Witschi et al., 1997) (see Chapter 10).

Several etiologic factors in COPD have been investigated with regard to cigarette smoking (Sethi and Rochester, 2000). One factor is airway hyperreactivity, measured by the provocation of airway constriction following inhalation of a bronchoconstricting drug or physical condition. Several longitudinal studies have shown that airway hyperreactivity is related to accelerated decline in lung function in cigarette smokers (Frew et al., 1992; Rijcken et al., 1995; O'Conner et al., 1995; Postma et al., 1986; Tashkin et al., 1996; Tracey et al., 1995). Hyperresponsiveness in the presence of blood eosinophilia increases the risk of developing respiratory symptoms (Jansen et al., 1999). If airway hyperreactivity plays a role in the progression of COPD, it is possible that regular use of bronchodilators may slow the rate of decline. However, this conclusion was not supported by the Lung Health Study (Anthonisen et al., 1994; see below).

est obstacle for developing a specific biomarker is the lack of fundamental information on mechanisms by which exposure to tobacco smoke causes specific respiratory diseases. Insight into understanding the molecular basis of diseases may come from unraveling the complex interactions between genetic makeup and the environment that could evolve from the Human Genome Project or similar molecular studies.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition and Epidemiology

Chronic obstructive pulmonary disease is an all-inclusive term that encompasses chronic bronchitis (the presence of chronic productive cough) and emphysema (permanent enlargement of the distal airspaces) (Aubry et al., 2000). Usually, chronic bronchitis and emphysema occur in combination. The major clinical features of COPD are chronic cough, expectoration of sputum, breathlessness during exertion, and airflow obstruction on forced expiration that tends to worsen over time (Barnes, 2000; Piquette et al., 2000).

The natural history of COPD and its health care implications have been extensively reviewed (Hensley and Saunders, 1989). The course of COPD is characterized by loss of ventilatory function from the peak attained in early adulthood (Figure 14-1). Clinical symptoms of COPD develop after substantial loss of ventilatory function, typically in the fourth and fifth decades of life. In longitudinal studies, the average loss of function in nonsmokers begins at about age 30 as assessed by the relationship of change in forced expiratory volume at 1 second (FEV_1) with age. In nonsmokers, this amounts to about 20 ml per year. The rate of decline in FEV_1 is somewhat greater (40 ml per year) in smokers of 30 cigarettes per day compared to nonsmokers (Fletcher and Peto, 1977; Camilli et al., 1987). A subset of smokers, who will develop COPD, lose function more rapidly (60 ml per year; Habib et al., 1987). However, there is variation in these rates and the rate of decline increases with age (Fletcher and Peto, 1977; Camilli et al., 1987). Smokers who cease smoking do not regain lost function, but the rate of decline of FEV_1 slows to that of nonsmokers (Burrows et al., 1990). Loss of lung function appears to be a risk factor for mortality even among never-smokers (Beaty et al., 1985; Ashley et al., 1975). A loss of lung function may reflect other diseases such as heart disease that decrease life expectancy (Beaty et al., 1985). The annual number of deaths attributable to chronic airway obstruction, bronchitis, and emphysema in the United States during 1990–1994 was 70,000 (Table 14-2). The relative risk of death from COPD in smokers who have symptoms is reduced by cessation, but remains almost as high as that of current smokers. Many of those who eventually die of COPD suffer from prolonged disability due to dyspnea, cough, and sputum production.

Table 14-1 Smoking-Affected Pulmonary Diseases

Disease Incidence or Severity Definitely Increased by Smoking
Common cold
Influenza
Bacterial pneumonia
Tuberculosis infection
Invasive pneumococcal infection
Pulmonary hemmorrhage
Pulmonary metastatic disease
Spontaneous pneumothorax
Eosinophillic granuloma
Respiratory bronchiolitis-associated interstitial lung disease
Idiopathic pulmonary fibrosis
Asbestosis
Rheumatoid arthritis-associated interstitial lung disease
Disease Incidence or Severity Possibly Decreased by Smoking
Sarcoidosis
Hypersensitivity pneumonitis

NOTE: Modified with permission from Murin, S., Smith Bilello, K., Matthay, R. 2000 Other Smoking-Affected Pulmonary Diseases. Clinics in Chest Medicine. 21:3, 121. Copyright (2000) by W.B. Saunders Company.

BIOMARKERS OF RESPIRATORY DISEASES

There are currently no specific biomarkers of respiratory disease due to smoking tobacco products (see Chapter 11). The rare genetic deficiency of α_1-antitrypsin is a risk factor for disease, not a biomarker (see below). No unique molecular or genetic defect specific for tobacco-related respiratory disease has been identified. The processes involved, such as inflammation and increased levels of oxidants, are not unique to tobacco-related respiratory diseases. Identifying unique biomarkers is further confounded by the heterogeneous nature of these diseases, the complex mixture that makes up tobacco smoke, and the range of individual susceptibilities to the harmful effects of tobacco smoke among users (see Chapter 11). In COPD, for example, the majority of smokers develop abnormal lung function (Camille et al., 1987), but only 15–20% will develop symptomatic COPD (Fletcher and Peto, 1977). There appears to be no specific clinical or physiological feature to predict which smokers exhibit a rapid decline in lung function (Habib et al., 1987). The most widely used markers of tobacco-related respiratory diseases in population studies are symptom questionnaires and pulmonary function testing. These have well-known limitations of specificity and sensitivity, particularly for detecting the early effects of tobacco smoke on lungs (U.S. DHHS, 1989). Subtle effects of tobacco smoke exposure on the lung can be detected by sampling fluid in the lower respiratory tract via a bronchoscope inserted into the airways, but the significance of these changes to clinically important pulmonary disease has not been established. Newer approaches such as sampling the subjects' urine (Pratico et al., 1998) or exhaled gas (Paolo et al., 2000; Ichinose et al., 2000) for metabolic products due to tissue injury have the advantage of noninvasive sampling but must be validated. Clearly, the great-

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Nonneoplastic Respiratory Diseases

In persons who smoke, the cells that line the bronchi and alveoli come into direct contact with high concentrations of tobacco toxicants. Not surprisingly, respiratory diseases such as chronic obstructive pulmonary disease (COPD) are major health problems in smokers (Murin and Silvestri, 2000). Tobacco-related respiratory diseases predominately affect male smokers, but the prevalence of COPD in women is rising rapidly and it appears to follow the prevalence of smoking by 20–30 years (Tanoue, 2000). Children exposed to environmental tobacco smoke (ETS) are also affected (Joad, 2000). Because low levels of tobacco toxicants from ETS come in direct contact with the lung, it is necessary to consider the health effects of both mainstream and secondary smoke.

In evaluating harm reduction strategies for tobacco-related lung diseases, three major nonneoplastic respiratory diseases linked to cigarette smoking must be considered: COPD, asthma, and respiratory infections. Numerous other respiratory diseases are strongly related to cigarette smoking as shown in Table 14-1 (Murin et al., 2000). The relative risks of mortality due to smoking-related nonneoplastic respiratory diseases are considerable, and approximately 91,000 Americans died annually of respiratory diseases attributed to smoking during 1990–1994 (Table 14-1 and 14-2) (Novotny and Giovino, 1998). Cigarette smoking is estimated to contribute to 80–90% of cases of COPD, and the amount and duration of cigarette smoking directly influence the progression of COPD. Asthma and respiratory infections, on the other hand, are not caused by tobacco smoke but are worsened by exposure to cigarette smoke. Of special importance in considering harm reduction strategies is the contribution of ETS to asthma and respiratory infections in children. Abatement strategies for susceptible children exposed to environmental tobacco smoke may differ from those used to reduce harm in tobacco smokers.

An extensive knowledge base exists describing the contribution of tobacco smoke exposure to nonneoplastic respiratory disease, and key points are described briefly here. The major goal of this chapter is to summarize studies designed to test whether reducing exposure to tobacco toxicants improves health outcomes for respiratory diseases. As will be described below, there are considerable gaps in information about reducing harm and uncertainties about the quality of the existing knowledge base in this regard. Consequently, a research agenda is proposed to guide future studies aimed at reducing the harm from smoking in COPD.